



# "Is the Copy Better than the Original? The Regulation of Orphan Drugs: a US-EU Comparative Perspective"

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# *Is the Copy Better than the Original?*

## The Regulation of Orphan Drugs: a US-EU Comparative Perspective

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### **ABSTRACT**

Today, more than 5,000 diseases are cataloged as “rare” by the scientific community, so long as they afflict small sections of population. Due to the lack of economic profitability, the pharmaceutical industry has been traditionally reluctant to invest time and money in developing and marketing drugs for these ailments, and such market failure had to be corrected by Government action in form of various incentives.

The US Orphan Drug Act of 1983 pioneered the regulation of this type of medicines, and its success encouraged other countries to enact similar legislation. Among these new orphan drug laws is the one that was drafted in the European Union in 2000. This paper attempts to scrutinize some of the key points of the initial American regulatory framework as well as the main criticisms that it received and to subsequently take a look at the responses that European authorities have devised to address such attacks to the American text. The overwhelming satisfaction surrounding US law may explain the great similarity with its European younger brother, even though the “copy” has tried to make some modest contributions from its own, for instance while addressing what perhaps is the most serious caveat of the law: the abuses by the industry that lead to high prices and “blockbuster orphans”. However, both jurisdictions still have some more aspects to ameliorate in order to create a more perfect set of incentives that may assure the availability of remedies for rare diseases striking a better balance between competition and innovation. Besides, some newly raised issues, like the necessity of international cooperation to address the challenges posed by a global pharmaceutical market and the need for extending the benefits of orphan drug legislation to so-called “third-world diseases”, are awaiting legal answers.

### **1.**

#### **Introduction.**

Today, there are more than 5,000 diseases, about 10% of the total number of human ailments, which the medical community considers to qualify for the label of “rare diseases,” affecting between 45 and 55 million people in the United States and the European Union alone<sup>1</sup>. Despite the heterogeneity of this category, rare disorders present a common feature: they are so unusual and infrequent that in most cases an appropriate treatment is not available<sup>2 3</sup>. The possible remedies for rare diseases are usually called “orphan drugs”<sup>4</sup>, since in normal market conditions no sponsor would show up as a parent to take them through the pre-market scrutiny by the regulatory agencies. Due to the small prevalence of rare diseases, the pharmaceutical industry is unwilling to “adopt” these treatments, so long as the foreseen sales and benefits are scarce, specially in view of the huge development costs required for getting a new drug into the market<sup>5</sup>. Confronting this problem, the governments of many countries have noticed the necessity of some form of public intervention that may assure orphan patients a remedy for their illnesses and act consequently. From a public policy perspective, the main action taken to assure the availability of these medicines has been the establishment of various publicly-sustained incentives in order for the pharmaceutical industry to market them in sufficient quantities. Roughly, these benefits may be classified in two groups. First, the hallmark incentive implemented by all the regulators in the various countries which have passed orphan drug laws has been the conferral of a so-called *market exclusivity* right to the “adopters” for a given number of years<sup>6</sup>, which prevent others from commercializing the same drug during this period, therefore increasing substantially the prospects of reaping the investment previously made. Yet, there is a second main group of incentives used to spur the production

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<sup>1</sup>Robin E. Margolis, *Is Orphan Drug Act Compromise Near?* 11 No.7 HealthSpan 21, 21 (1994); Thomas Maeder, *The Orphan Drug Backlash*, 288 (5) Sci. Am. 80, 82 (2003); Françoise Grossetête, “Research and Development of Orphan Drugs: at Last a European Regulation” in *The European Regulation on Orphan Medicinal Products*, 3 Pharmaceuticals Policy and Law 7, 7 (2001). Other authors suggest that the total number of rare disorders should be reviewed, and may actually reach 8,000. Erik Tambuyzer, *The European Orphan Medicinal Products Regulation and the Biotechnology-based Industry in Europe*, 6 Journal of Commercial Biotechnology, 340-344 (2000).

<sup>2</sup>Alvaro Lavandeira, *Orphan Drugs: legal aspects, current situation* 8 Haemophilia 194, 195-196 (2002). Among these rare diseases it is possible to cite different varieties of tumors like ovarian cancer or many kinds of leukemia, some AIDS-related opportunistic diseases, and genetic diseases such as cystic fibrosis. The National Organization of Rare Diseases (NORD) web page contains a highly detail database of rare disorders at <<http://www.rarediseases.org>>.

<sup>3</sup>All countries which have drafted orphan drug legislation tend to use prevalence, that is, number of people affected by a particular disease, to select those ailments for which orphan drugs may be designated. The World Health Organization considers as being rare disorders only the diseases that affect 0.65-1 out of every 1,000 people. Lavandeira, *supra* note 2, at 195-196.

<sup>4</sup>Orphan drugs can be generally defined as “drugs intended to treat rare diseases whose potential sales are not large enough to justify funding of the necessary animal and clinical tests”. Peter B. Hutt & Richard A. Merrill, *Food and Drug Law: Cases and Materials*, 566 (2<sup>nd</sup> ed. 1991).

<sup>5</sup>It has been estimated that it costs on average around \$300 million dollars and takes not less than a decade to market any drug. Gary A. Pulsinelli, *The Orphan Drug Act: What's Right with It* 15 Santa Clara Computer & High Tech. L.J. 299, 304 (1999).

<sup>6</sup>The length of the exclusive marketing rights varies from country to country, in a range that goes from the ten-period chosen by the European rules and the Japanese Orphan Drug Program to the seven years used by the US Orphan Drug Act. Paola Minghetti et al. *A Proposal to Improve the Supply of Orphan Drugs*, Pharmacological Research, Vol. 42, no.1, 33-35 (2000)

and marketing of orphan medicinal products which encompasses, among others, grants and subsidies to finance the various clinical trials required to prove the safety and effectiveness of the drug, waivers of various administrative fees, tax credits and diverse means of support and administrative guidance by the public agencies through the whole process.

While approaching the regulation of orphan medicinal products, it should be noted that what the orphan drug rulemakers are dealing with is the intersection between market and health. Orphan legislation tries in essence to provide an equal access to health to all people that suffer from any disease, no matter its nature. Governments have recognized the limits of the market to supply society with a remedy for every single disease, and thus took a step forward to avoid an scenario where the access to health protection would depend on how many fellow citizens present the same problem, or, to put it in other terms, on how profitable is the drug a particular patient needs. Orphan legislation is thus a solution designed to address this very conflict between medicine and economics by pushing toward the right of all citizens to a certain level of health protection<sup>7</sup>.

This paper tries to identify the main concerns and critiques that have arisen from the U.S. experience since the drafting of the Orphan Drug Act of 1983 and to examine the responses that its “younger brother” in the European Union has offered to tackle all these controversial points. Three main topics will be covered in different sections, in addition to a final set of conclusions. In the first place, section 2 deals with the historical background of the actual regulations on both sides of the Atlantic ocean, from the appearance of the first laws in the United States to the translation to legal terms of the European policy in 2000. It also encompasses a description of the main characteristics of the regulatory schemes implemented in the different countries, with special attention to both the US and the EU. Section 3 consists basically of a general assessment of the practical outcomes produced by these legal frameworks in each side of the Atlantic Ocean. Section 4 constitutes the core of this work, specifically addressing all the purported caveats and contentious points identified by commentators, industry and patients within the American system; and referring to how the European authorities have faced these challenges. Finally, Section 5 provides some conclusions in light of the comparative analysis of both jurisdictions described before.

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<sup>7</sup>The “right to health” has been recognized in a variety of international texts on human rights, such as the Universal Declaration of Human Rights of 1948 (article 25.1) or the 1961 Social Charter of the Council of Europe (article 11). For a general discussion on these issues, cf. Lavandeira, *supra* note 2, at 194-195.

## 2.

### **The Treatment of Rare Diseases and the Birth and Raise of orphan drug legislation.**

The birth of the orphan drug laws took place in the United States during the early 80s. The US Orphan Drug Act of 1983<sup>8</sup> has been the model for other countries when addressing the regulation of orphan medicinal products. This piece of legislation has internationally been recognized as a “booster” for the introduction of orphan medicinal products<sup>9</sup>, and happened to be widely used as a model for a sound orphan drug policy in many other countries. Today, nations like Japan, Korea and Australia have orphan drug legislation drawn in mostly from the American text<sup>10</sup>. However, the most important step taken towards a worldwide regulation on orphan medicinal products was the drafting of appropriate rules in the European Union via Regulations in 1999-2000. The US and the EU (without the 10 new countries entering as of May 1, 2004) account for nearly 75% of R&D for pharmaceuticals and biologics and represent two-thirds of the world pharmaceutical market<sup>11</sup>. In light of this data, the importance of both legal frameworks on orphan drugs seems obvious, and mutual feedback appears to be a necessity to enrich both systems and promote global cooperation.

The purpose of this section is to explore the historical development of orphan drug laws, from the US Orphan Drug Act to the recent implementation of the European Policy on the field.

### 2.1.

#### **The Beginning: the US Orphan Drug Act of 1983 and its History.**

This story begins in the early 80s, when American public opinion became increasingly concerned about the situation of millions of fellow citizens suffering from rare diseases. Congress began to consider taking action to resolve the orphan drug problem, holding hearings starting in 1980, in the midst of strong advocacy

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<sup>8</sup>Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1982) (codified as amended at 21 U.S.C. §§360aa-360ee (1994), 26 U.S.C. §45C (Supp. II 1994), 42 U.S.C. §236 (1994).

<sup>9</sup>*Cf.* as an example, Josep Torrent Farnell & Rosa Morros, “The EU Challenges on the Designation of Orphan Medicinal Products”, in *European Regulation on Orphan Medicinal Products*, 3 Pharmaceuticals Policy and Law 19, 19-20 (2001).

<sup>10</sup>Minghetti et al., *supra* note 6, at 34.

<sup>11</sup>Christopher-Paul Milne et al., *Orphan Drug Laws in Europe and the US: Incentives for the Research and Development of Medicines for the Diseases of Poverty*, Commission of Macroeconomics and Health of the WHO Working Paper no. WG2:8, 4; available in English at [http://www3.who.int/whosis/cmh/cmh\\_papers/e/papers.cfm?path=cmh,cmh\\_papers&language=english](http://www3.who.int/whosis/cmh/cmh_papers/e/papers.cfm?path=cmh,cmh_papers&language=english)

efforts by patient organizations like NORD, the support of the medical profession, stark opposition by the pharmaceutical industry and the reluctance of the FDA itself, which preferred to deal with the problem through a more flexible application of the general administrative requirements<sup>12</sup>. The Act was finally enacted in December 1982<sup>13</sup>, laying out the basics of the first specific orphan drug policy ever adopted in the world.

The 1983 Act defined orphan drug by referring to the concept of “rare disease or condition” in the United States, which in turn was defined as any ailment which is so uncommon that “there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug”<sup>14</sup>. The only criteria for designation used in the original version of the Act was therefore the economic viability of the drug represented by the expected revenues from sales not covering the costs. Besides, any orphan drug which deserved this denomination under the original text had to be unpatented or unpatentable under the patent laws, since Congress believed that these norms afforded enough protection for the investment to be made and consequently there was no need for further legal shield. Once these requisites were met, the Act provided that FDA should confer the product a designation as “orphan drug”, immediately benefiting from all the incentives laid down. Although we will revisit this issue later on when discussing the practical outcome of the law and its alleged flaws, a brief account of the advantages embodied in the Orphan Drug Act for all designated products were as follows<sup>15</sup>:

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Seven years of market exclusivity for the designated orphan indication of the product. During this time, no identical and competing product will receive marketing authorization from FDA<sup>16</sup>;

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<sup>12</sup>David B. Clissold, *Prescription for the Orphan Drug Act: the Impact of FDA's 1992 Regulations and the Latest Congressional Proposals for Reform* 50 Food & Drug L.J. 125, 127-128 (1995), citing various Congressional hearings.

<sup>13</sup>As a curiosity, some commentators have suggested that the definitive catalyst for the introduction of the Act was the wide public reaction to an episode of the TV show Quincy, M.E. broadcasted in March 1981, showcasing the story of a boy with Tourette's syndrome. Pulsinelli, *supra* note 5 at 305.

<sup>14</sup>Orphan Drug Act, Pub. L. No. 97-114, §526(a)(2), 96 Stat. 2049 (1982) (codified as amended at 21 U.S.C. §360bb(a)(2) (1994)).

<sup>15</sup>In addition to all these incentives, the Orphan Drug Act also created the so-called “Orphan Products Board” (OPB), depending of the Department of Health and Human Services, as the body in charge of the coordination and control of all governmental policies and programs in the field. As Pulsinelli points out, many of the expected tasks of the OPB are actually under the FDA's Office of Orphan Product Development (e.g. the management of the grant program). Pulsinelli, *supra* note 5 at 313.

- Federal grants to fund clinical trials of designated orphan products and protocol assistance by the FDA<sup>17</sup>;
- Tax credits for such clinical trials.<sup>ALG</sup>Antón Leis García

During the first year after the Act came into effect, it became apparent that the response of the industry was not what the legislators initially expected<sup>18</sup>, particularly due to the heavy burden that producers faced to demonstrate the costs of the intended orphan drugs to show that market conditions would render them unprofitable<sup>19</sup>. The legislative response was the 1984 Amendment to the Act, which modified the text to add a presumption of unprofitability when the disease or condition has a patent population of less than 200,000 in the United States, which remains today in the text of Section 526 of the actual version of the Act<sup>20</sup>.

In 1985, the second main amendment of the Act took place. Congress changed the text to apply market exclusivity protection to patented and patentable drugs, in an attempt to increase protection to products with a patent life about to be over<sup>21</sup>. Besides, determining whether a particular drug was patentable or not lead in fact to delays in the designation of orphan drugs, provided that in some cases assistance by the Patent and Trademark Office was required<sup>22</sup>.

Despite many further attempts that will be discussed in the fourth section of this paper, the last amendment to the Orphan Drug Act occurred in 1988. Congress had then to repair various errors and to reauthorize some provisions that were close to expiring (e.g. grant appropriations). Some other minor rules of administrative nature were introduced, for instance the one that requires sponsors to notify the FDA any interruption in

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<sup>17</sup>“Protocol assistance” refers to permanent guidance and support provided by FDA to sponsors during the investigations leading to final market approval. Bear in mind that the reduced prevalence of market diseases poses several obstacles for producers to develop accurate and effective clinical trials. Open protocols happened to be a solution to this problem by allowing the manufacturer to supply patients not participating in the clinical trials with the drug while they are still in progress, and therefore were laid down in Section 528 of the Act. *Id.* 311-312.

<sup>18</sup>During this first year, only 15 requests were filed from which 10 lead to designated products. *Cf.* generally Orphan Drug Act Oversight Hearings Before the Subcommittee on Health and Environment of the House Committee on Energy and Commerce, 98<sup>th</sup> Cong., 2<sup>nd</sup> Sess. 719 (1984).

<sup>19</sup>Clissold, *supra* note 10 at 128-129; David Duffield Rohde, *The Orphan Drug Act: an Engine of Innovation? At What Cost?* 55 Food & Drug L.J. 125, 129 (2000).

<sup>20</sup>The establishment of this “bright-line rule” was regarded with some concern by many observers, such as the Office of Management and Budget (OMB), so long as it might lead to abuses with regard to highly-priced drugs. *Id.* at 129. This kind of fears have been constant since the Orphan Drug Act was passed, and have lead to passionate discussions that we will address in subsection 4.1 below.

<sup>21</sup>*Id.* at 130.

<sup>22</sup>Pulsinelli, *supra* note 5 at 308. The 1985 amendment also expanded the scope of the Act to include antibiotics and provided for research grants to cover all “qualified testing” instead of just “qualified clinical testing”, also prorogating these grants or the following three years. *Id.* 308.

the manufacturing of any approved orphan product at least one year in advance<sup>23</sup>.

The regulatory scheme was not complete until January 1993, when the FDA approved and put into effect the definitive version of the so-called *Orphan Drug Regulations*<sup>24</sup>, which established express rules on the administrative procedures for obtaining an orphan drug designation and clarified some traditional problems regarding the wording of the Act, in particular those related to the criteria used to consider a drug “different” from another with regard to market exclusivity right, and to the meaning of “clinical superiority” as an exception to such a right<sup>25</sup>. These issues will be reviewed in depth in Subsection 4.2., while discussing some of the controversies arising from certain ambiguities of the law.

The three main amendments of the Orphan Drug Act described above (1984, 1985 and 1988) are only a few of the proposed modifications of the statute that have come under public scrutiny during the last twenty years. There have been other several different attempts to change the letter of the law that have triggered no tangible results<sup>26</sup>. These proposals will be discussed below when dealing with the various critiques received by the actual system, so long as they tried to correct some of the alleged deficiencies detected in the 1983 Act.

## 2.2.

### The International Spread of Orphan Regulations.

The tremendous success that the American orphan drug legislation experienced specially once the initial reluctance of the industry was overcome after the 1984 amendments induced other governments to put in place similar programs that may enable the industry to produce and market drugs for the treatment and diagnosis of rare diseases<sup>27</sup>. Different governments began to adopt different and sometimes isolated

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<sup>23</sup>Orphan Drug Act., Pub. L. No. 97-114, §526(b)(1), 96 Stat. 2049 (1982) (codified as amended at 21 U.S.C. §360bb(b)(1) (1994)).

<sup>24</sup>57 Fed. Reg. 62,076 (Dec. 29, 1992). The initial Notice of Proposed Rulemaking was published almost a year before (56 Fed. Reg. 3,338 (Jan. 29 1991)).

<sup>25</sup>The 1993 Regulations embody as well some norms over the information disclosure obligation applying to all sponsors in order for them to effectively show that their products fall within the definition of “orphan drug” described above (21 C.F.R. §316.29(a) (1998)).

<sup>26</sup>The two main initiatives to amend the Orphan Drug Act took place in 1990 and 1994. The former amendment was vetoed by President George H. Bush and the later was not even enacted.

<sup>27</sup>For a general discussion on comparative orphan drug programs, cf. Mae Thamer et al., *A Cross-national Comparison of Orphan Drug Policies: Implications for the U.S. Orphan Drug Act* in 23 J. Health Pol. Pol’y & L. 265 (1998).



measures<sup>28</sup>, and later embarked on comprehensive legislative initiatives.

Japan kicked off its orphan drug program in October 1993 by amending the Pharmaceutical Affairs Law and other ancillary regulations and setting up a complete system for orphan products designation and a full catalog of incentives for their development and marketing<sup>29</sup>. Orphan products are initially reviewed by the Pharmaceuticals and Medical Devices Evaluation Center and the Central Pharmaceutical Affairs Council and later designated by the Minister of Health and Welfare. The designation criteria is not only based exclusively on prevalence (less than 50,000 patients in Japan, <0.04% of the population<sup>30</sup>), but also on the high probability of development as shown by data provided by the sponsor and the inexistence of equivalent alternative, i.e. with the same or superior efficacy or safety<sup>31</sup>. The Japanese program provides for a 10-year period of market exclusivity, coupled with some other incentives (e.g. grants, tax deductions, consultations with the agency and fast track review of approval)<sup>32</sup>. So far, Japanese authorities have designated 167 orphan drugs and 10 devices, as published in the web page of the Japanese Organization for Pharmaceutical Safety and Research <sup>33</sup>.

Australia has also implemented a “robust but still incipient” orphan drugs program<sup>34</sup>. The Australian Government has recently introduced via an interagency agreement an automatic recognition mechanism that allows the orphan products designated as such in the United States by the FDA to reach the Australian market almost immediately. In 1997, a comprehensive Orphan Drug Policy was drafted and implemented<sup>35</sup>.

### 2.3.

#### **The Orphan Laws Cross the Atlantic: the European Union Approach to Orphan Drug Regulation.**

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<sup>28</sup>For instance, Singapore established, with FDA assistance, an importation exemption for orphan medicinal products designated by recognized foreign regulatory agencies that intend to enter the country. Marlene E. Haffter, “Rare Diseases and Orphan drugs”, in *European Regulation on Orphan Medicinal Products*, 3 Pharmaceuticals Policy and Law 37, 38 (2001).

<sup>29</sup>Mamoru Narukawa, “Japanese Approach to Orphan Drugs”, in *European Regulation on Orphan Medicinal Products*, 3 Pharmaceuticals Policy and Law 41, 41 (2001).

<sup>30</sup>Minghetti et al., *supra* note 6, at 34-35.

<sup>31</sup>Narukawa, *supra* note 29, at 41.

<sup>32</sup>*Id.* 41-42.

<sup>33</sup>*Cf.* <<http://www.kiko.go.jp/download/ListofOrphanProducts20040213.xls>> (last accessed: February 29<sup>th</sup> 2004).

<sup>34</sup>Milne et al., *supra* note 11, at 4.

<sup>35</sup>Lavandeira, *supra* note 5, at 197. The Australian regulations provide for an exclusive marketing period of 5 years and the exemption of the normal fees charged by the Therapeutic Goods Administration for the approval of any drug. *Cf.*, generally, Department of Health and Aged Care, *The Orphan Drug Program and Improving Community Access to Effective Drugs for Rare Diseases* (2001), at <<http://www.health.gov.au/tga/docs/pdf/orphrev.pdf>>.

Some member States of the European Union had been active during the 90s taking some actions towards a broad regulation on orphan medicinal products, even before any initiative was promoted at the Community level<sup>36</sup>. A public debate within the European institutions ensued regarding the convenience of following in US footsteps on the field through a comprehensive regulation covering the Common Market as a whole.

Rare diseases have been a focus of attention for the European Commission since 1994, when the BIOMED 2 program, within the context of the 4<sup>th</sup> Framework Program for research and technological development (1994-1998) provided funding for 23 research projects up to a total appropriation of Å8.65 million<sup>37</sup>. Moreover, rare conditions were further classified as a “priority area” for Community action in the context of the Framework for action in the field of public health<sup>38</sup>, after the Commission presented a proposal of Decision of the European Parliament and the Council adopting a program of community action for the period 1999-2003 on rare diseases<sup>39</sup>.

On July 27 1998, the European Commission published its proposal for a European Parliament and Council Regulation on orphan medicinal products<sup>40</sup>. At the European Parliament, the Committee on the Environment, Public Health and Consumer Protection issued a report amending in first reading proposal in terms that were not accepted by the Commission<sup>41</sup>. The second proposal was approved by the Parliament in a plenary session held in December 1999 and by the Council. That was the birth of *Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan medicinal products*<sup>42</sup> (hereinafter “Regulation 141/2000”), the basic norm outlining the European policy on the field of rare dis-

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<sup>36</sup>This was the case of France, whose Government included orphan medicine development as a priority subject within the Cabinet program for the European Union in 1995 during the French Presidency of the Council. The Health Minister at that time, Mme. Simone Weil also created a ministerial mission concentrated in orphan drug policy, gathering an important amount of expertise on the field. European Foundation for the Advancement of Medicine, *Workshop on “Rare Diseases and Orphan Drugs: European Perspective”*, Brussels, May 5 1998, [hereinafter *Workshop on Rare Diseases and Orphan Drugs*], intervention by Annie Wolf, 30-31.

<sup>37</sup>Bruno Hansen, “Perspective from the European Commission”, in *European Regulation on Orphan Medicinal Products*, 3 Pharmaceuticals Policy and Law 43, 43 (2001). Budgetary provisions for research in the treatment of rare diseases were also included in the Fifth Framework Program (1998-2002)

<sup>38</sup>COM (1993) 559 final & COM (1997) 225 final.

<sup>39</sup>OJ L 155, 22.6.1999, p.1, Decision No 1295/1999 EC of the Parliament and the Council of 29 April 1999 adopting a programme of Community action on rare diseases within the framework for action in the field of public health (1999 to 2003).

<sup>40</sup>COM (1998) 450 final. The aim of the proposal was described in the text itself as “[establishing] a Community procedure for designating orphan medicinal products and to introduce incentives for orphan medicinal products research, development and marketing, in particular by granting exclusive marketing rights for a ten year period”.

<sup>41</sup>Report on the proposal for a European Parliament and Council Regulation on Orphan Medicinal Products. A4-0078/99. Rapporteur: Christian Cabrol. For a complete list of the changes proposed and a description of the procedures before the final version of the Regulation was published *cf.*, José Luis Valverde, “Editorial” in *European Regulation on Orphan Medicinal Products*, 3 Pharmaceuticals Policy and Law 1-5 (2001).

<sup>42</sup>OJ L 18, 22.1.2000, p.1. The final version was highly coincident with the initial proposal by the Commission.

eases and orphan drugs, which entered into force on April 28<sup>th</sup> 2000. Commission Regulation (EC) No 847/2000, of 27 April 2000, laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts “similar medicinal product” and “clinical superiority”<sup>43</sup> (hereinafter “Regulation 847/2000”), followed to precise some procedures and concepts advanced in Regulation 141/2000. The aim of the initiative was clear: to provide, in similar fashion to the US Orphan Drug Act, an attractive environment for the pharmaceutical industry to develop and market drugs for rare diseases in the European Union<sup>44</sup>. The obvious ties to the American regulation were expressly recognized throughout the entire drafting process<sup>45</sup>.

The scope of Regulation 141/2000 is limited to “medicinal products for human use” within the meaning of Directive 65/65/EEC<sup>46</sup>, which refers in turn to any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or for treating or preventing a disease”. From this wording, it is important to note that while vaccines fall squarely within breath of the regulation, medical devices and nutrition supplements are not covered, similarly to the initial version US regulation<sup>47</sup>.

Article 3.1 of the Regulation establishes the criteria for designation of orphan medicinal products, which combine a epidemiological feature (prevalence figure in the total Community population of less than 5 per 10,000)<sup>48</sup> with an economic test (alleged economic unviability). Either element must be established by the sponsor, who is also obligated to show that there is no “satisfactory” method of diagnosis, prevention or

<sup>43</sup>OJ L 103, 28.4.2000, p.5. This complementary Regulation is specific about the criteria for designation (i.e. prevalence, potential for return on investment and existence of other methods of diagnosis, prevention or treatment), setting detailed rules on the required data. It also fixes a detailed set of definitions for terms laid down in the Regulation 141/2000, such as “significant benefit” or “clinically superior”. This issues will be revisited throughout Section 4.

<sup>44</sup>Preamble of Regulation 141/2000. OJ L 18, 22.1.2000, p.1.

<sup>45</sup>*Cf.*, for instance, the Explanatory Memorandum that headed the initial Proposal of Regulation adopted by the Commission. *Supra* note 40.

<sup>46</sup>Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action related to medicinal products. OJ 22, 9.2.1965m p. 369 (Directive as last amended by Directive 93/39/EEC at OJ L 214, 24.8.1993, p.22).

<sup>47</sup>Recall that Japan did include medical devices within its orphan product program. *Cf. supra* note 33. Recently, the US Orphan Drug Program was expanded to include medical foods and devices that meet the orphan criteria set out in the Orphan Drug Act. Milne at al., *supra* note 11, at 5. As for medical devices, the “Orphan Product Development Program” and the Humanitarian Device Exemption embodied in the Safe Medical Device Act of 1990 but created in 1996, and detailed by FDA regulations have implemented a system that strikingly resembles that of the Orphan Drug Act. Brigitte Casteels-Rappagliosi, “Rare diseases and medical devices in the European Union”, in *European Regulation on Orphan Medicinal Products*, 3 Pharmaceuticals Policy and Law 69, 71-72 (2001).

<sup>48</sup>Note that this ratio is below the benchmark ruling in the US (7.5 per 10,000) and slightly over the Japanese (4 per 10,000). Emer Cooke, “The European Regulation on Orphan Medicinal Products” in *European Regulation on Orphan Medicinal Products*, 3 Pharmaceuticals Policy and Law 11, 13 (2001).

treatment of the condition in question or, if such method exists, that the medicinal product will provide patients with “significant benefit”<sup>49</sup>. Importantly, the condition targeted by the drug must be a “life-threatening, seriously debilitating or serious and chronic” ailment, and the indication of the drug must be medically plausible.

Article 4 cope with the institutional design of the European orphan drug policy. A new body within the European Agency for the Evaluation of Medicinal Products (EMA)<sup>50</sup> was created: the Committee of Orphan Medicinal Products (COMP), whose two main missions are the examination of any application for the designation of a medicinal product as an orphan drug, and the assistance to the Commission on any matter in relation with the Community policy on orphan drugs. One of the interesting features of this new organization is that among its members, three (from a total of 21 plus a Chairperson) are designated by the European Commission to represent patients’ organizations, which warmly welcome this attempt to provide those who are the final recipients of the regulation with a voice on their own to offer their positions during the rulemaking and administration of the whole program<sup>51 52</sup>.

The designation procedure laid out in Article 5 is purportedly “rapid and flexible”<sup>53</sup>. Applications should be addressed to the Agency Secretariat, which, in coordination with a rapporteur, processes the file. The COMP has to deliver its opinion in 90 days from the Secretariat’s validation of the application. EMA then forwards the opinion to the European Commission and the sponsor, who in the event of a negative decision may file an appeal before the COMP<sup>54</sup>. The European Commission shall take all final decisions 30 days after its reception, but they rarely differ from the initial opinions by the COMP<sup>55</sup>. With a favorable decision by

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<sup>49</sup>Article 3.2 refers the implementation of the first paragraph to the Commission. Commission Regulation 847/2000 happens to fulfill this requirement. Cf. generally Communication from the Commission on Regulation (EC) no 141/2000 on orphan medicinal products, OJ C 178, 29.7.2003, p.2.

<sup>50</sup>For a general discussion on the role of COMP and EMA, cf. Patrick Le Courtois & Melanie Carr, “Orphan Medicinal Products: the Role of the EMA” in *European Regulation on Orphan Medicinal Products*, 3 Pharmaceuticals Policy and Law 31-35 (2001).

<sup>51</sup>Cf. *Workshop on Rare Diseases and Orphan Drugs*, interventions by Abbey Meyers (23-24) and Stéphane Korsia (25-27), representing patients’ organizations in the US and Europe.

<sup>52</sup>The COMP is actually presided by a Spanish physician, Professor Josep Torrent Farnell, and encompasses 21 full members designated by either the member states or the Commission. There are also observers by various organizations, as well as from the acceding countries. <<http://www.emea.eu.int/hums/general/contacts/COMP.html>> (last accessed: February 29<sup>th</sup> 2004).

<sup>53</sup>Cooke, *supra* note 48, at 14. However, significant delays occur between designation and final marketing authorization (cf. discussion in 4.7. over the so-called “regulatory lag”).

<sup>54</sup>EMA recently released a set of rules on the internal procedure for Orphan Medicinal Product Designation, where the above-described process is detailed. EMA/8212/00/Rev 1. Also available at <<http://www.emea.eu.int/pdfs/human/comp/821200en.pdf>>.

<sup>55</sup>Cooke, *supra* note 48, at 14.

the Commission, the candidate product shall be entered in the Community Register of Orphan Medicinal Products, thereby acquiring all the benefits and privileges inherent to the condition of “designated orphan medicinal product”<sup>56</sup>.

The set of incentives and benefits accruing to designated orphan medicinal products in the European Union are established in Articles 6 through 9 of the Regulation 141/2000. Some of them are parallel to similar measures in the US regulatory framework, such as the scientific advice provided via “protocol assistance,” the fee waivers, and most notably the market exclusivity rights.

Protocol assistance in the Regulation 141/2000 tries to tackle the several specific problems that rare diseases and orphan drugs pose in relation with the viability of accurate trials and research. The Scientific Advice Working Group (SAWG) within EMEA is the body in charge of providing such assistance through a continuous feedback between the sponsors, a full network of external experts and the SAWG itself<sup>57</sup>. This assistance goes on between designation and marketing approval and indeed continues after the orphan drug is introduced into the market<sup>58 59</sup>.

Designated orphan medicinal products are also eligible for fee reductions for all charges payable under Community rules on drug marketing authorization<sup>60</sup>. This includes fees for both pre-authorization activities such as protocol assistance and for all actions under the market centralized procedure, i.e., application for marketing authorization before the EMEA (as distinguished from the marketing authorization obtained from one Member State authority, which allows commercialization all across the EU territory due to the principle of mutual recognition), post-authorization activities (e.g. annual fees) and the like<sup>61 62</sup>.

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<sup>56</sup>Article 5 paragraphs 11 and 12 deal with the transfer and removal of the designation. Interestingly, once it is demonstrated that the requisites of Article 3 are not longer met in respect of the particular product before the market authorization, such product will be effectively removed from the Register (Article 5.12(c)).

<sup>57</sup>*Cf.* generally, EMEA Guidance for Companies Requesting Protocol Assistance, EMEA/H/238/02 Rev.1, also available at <<http://www.emea.eu.int/pdfs/human/sciadvise/023802en.pdf>>.

<sup>58</sup>*Id.* at 2.

<sup>59</sup>As of February 2003, SAWG had received 18 new applications for Protocol Assistance. EMEA, *Report on the First 3-year mandate of the Committee for Orphan Medicinal Products: April 2000 – April 2003*, EMEA/9118/03, also available at <<http://www.emea.eu.int/pdfs/human/comp/911803en.pdf>> [hereinafter, “EMEA Report”], 25.

<sup>60</sup>Marketing authorization procedures are laid down in Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products. OJ L 214, 24.8.1993, p.1.

<sup>61</sup>EMEA Public Statement on Fee Reductions for Designated Orphan Medicinal Products, EMEA/H/4042/01 Rev. 4, 1, also available at <<http://www.emea.eu.int/pdfs/human/comp/404201en.pdf>>.

<sup>62</sup>The budgeting appropriations available for fee exemptions during year 2003 amounted to €3,300,000, which enabled EMEA to apply a reduction of 100% of the value of Protocol Assistance fees and 50% in all other cases. *Id.* 1. EMEA had requested

Finally, the EU law also included market exclusivity as the North star in the constellation of incentives for orphan medicinal products, the crucial element to assure availability of orphan drugs<sup>63</sup>. Although this particular issue will be examined deeply throughout Section 4, it is possible to suggest that the protection is only granted when the drug has been designated as orphan medicinal product by the Commission, and when marketing authorization has been issued by either the Community or all the 15 states (Article 8.1). This “shield” prevents EU and national authorities from granting a marketing authorization for the “same product” defined in terms of the same active substance and for the same indication within the following 10 years<sup>64</sup>. The duration of the protection may however be reduced to 6 years in the event that the criteria used for designation no longer apply. Indeed, exclusive rights may be interrupted in two cases: when the holder of those rights is unable to meet the demand of the product with enough quantities thereof, and when another applicant is able to establish that this own version of the drug is “safer, more effective or otherwise clinically superior”<sup>65</sup>. Regulation 847/2000 elaborates a bit on this vague concepts, solving (or attempting to do so) some huge practical problems, as Section 4 of this essay describes in more detail.

Two main incentives provided in the United States, specific grants funding clinical and nonclinical trials and tax credits, are lacking in the European regulatory scheme. The explanation for the absence of the latter is straightforward: the European institutions have no power on taxation regulations other than on those related to indirect levies and customs duties<sup>66</sup>. The application of tax benefits to orphan drug sponsors is deferred therefore to the member States, among which some have decided to do so<sup>67</sup>. With regard to grant programs, the approach taken in Europe has been different from the one in the US. Instead of funding clinical and nonclinical trials of designated drugs, the European authorities have included rare diseases as one of the priorities of broader programs on research and development programs that frequently encompass different kinds of subsidies and funding. The above-mentioned 4<sup>th</sup> Framework Program initiated a path carried on today by the 6<sup>th</sup> edition of the same initiative (applied since the beginning of 2004), which support investigational activities on rare diseases within the thematic priority “Life, science, genomics and biotechnology for health”<sup>68</sup>. Therefore, neither the EMEA nor any other entity within the Community provides sponsors

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<sup>63</sup>Cooke, *supra* note 48, at 15.

<sup>64</sup>*Id.*, at 15-16.

<sup>65</sup>Article 8.3(a) also provides for marketing by non-holders of exclusive rights under its consent.

<sup>66</sup>*Cf.* Articles 95-99 of the European Community Treaty. OJ C 325, 24.12.2002, p.1 (consolidated version after the Treaty of Nice).

<sup>67</sup>France and the United Kingdom have created specific tax credits for orphan drug research and development enterprises. The Netherlands applies to orphan drug sponsors the same benefits accruing to companies that foster and use any type of high technological research. EMEA Report, *supra* note 59, at 39-40.

<sup>68</sup>*Id.* at 26. *Cf. supra* note 37.

with specific grants for orphan drug R&D. Nevertheless, Article 9 of the Regulation 141/2000 makes clear that designated medicinal products shall be “eligible for incentives made available by the Community [...] to support research into, and the development and availability of, orphan medicinal products and in particular aid for research for small- and medium-sized undertakings provided for in framework programs for research and technological development”. Summing up, orphan drug research has a priority consideration by general EU R&D funding plans, but lacks any equivalent, at least at the Community level, to the FDA comprehensive grant program.

The European regulators decided to include among the set of incentives trying to promote the availability of orphan medicinal products an expedited access to the centralized marketing authorization procedure<sup>69</sup>. However, this purported “fast track” approval has not been able to keep the system from suffering what commentators term “regulatory lag”, that is, the existence of a significant lapse of time between designation and market approval.

The EU regulatory framework is complemented by the initiatives implemented by the 15 member States, which have been appearing since Regulation 141/2000 and even before<sup>70</sup>. Most of these measures have been for the most part either the above-mentioned tax credits or the reduction of fees required through various administrative procedures. Some countries have also adopted rapid authorization mechanisms similar to those set out at the Community level (e.g. Germany). In 2001, the Direction General Enterprise of the European Commission published an Inventory with all the measures adopted at both European and national levels on orphan medicinal products, thereby fulfilling the requirement of Article 9.3, which required the Commission to take such action<sup>71</sup>.

### 3.

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<sup>69</sup>Recall that there are also partial exemptions for paying the fees associated with the entire marketing process. Cooke, *supra* note 48, 15. Article 7 of the Regulation 141/2000 exempts designated orphan drugs from demonstrating that they comply with all the requirements laid down by Annex to Regulation (EEC) 2309/93. However, as Cooke points out, “in most cases an orphan medicinal product will indeed meet the criteria set out in that Annex, either because it has been produced by biotechnology [...] or because the medicinal product is regarded as being of “significant therapeutic importance”. Cooke, *supra* note 48, at 15.

<sup>70</sup>As of April 2003, all 15 Member States, with the only exceptions of Greece and Luxembourg have applied some sort of complementary incentives to the ones laid down at the Community level. EMEA Report, *supra* note 59, at 39-40.

<sup>71</sup>DG Enterprise, *Inventory of Community and National Incentive Measures to Aid the Research, Marketing, Development and Availability of Orphan Medicinal Products*, released on June 1<sup>st</sup> 2001 and periodically reviewed. Last version can be found at <<http://pharmacos.eudra.org/F2/orphanmp/doc/inventory/Inventory-en.pdf>>.

## How Well Is the System Working? The Need for Avoiding Self-indulgence.

The US Orphan Drug Act has 20 years of successful experience. Since it came into force in 1983, 1305 designations have been issued, from which 250 resulted in final marketing authorizations by the FDA<sup>72</sup>. This data may be compared with the 58 drugs that would have qualified for orphan status in the 17 years before the Act was passed<sup>73</sup>. Moreover, not less than 9 million American patients have benefited from the availability of these remedies throughout the period of implementation of the orphan drug laws<sup>74</sup>. All these numbers have triggered a highly positive opinion amongst patient organizations, professionals and legislators. Indeed, the pharmaceutical industry progressively abandoned its initial lack of enthusiasm from the moment the 1984 Amendments were passed<sup>75</sup>.

The American experience also produced some indirect benefits. The set of incentives laid down in the Orphan Drug Act has proven to be specially advantageous for the biotechnology industry in general and research and development in particular. Biotechs often resort to venture capitalists in order to finance their investment, and the monopoly profits coupled with market exclusivity rights appear to provide great incentives for such a financing, particularly in view of the fact that patent protection for biotechnological products is cloaked in uncertainty<sup>76</sup>. In fact, from 1983 to 1992 19% of all orphan drug approvals went to biotech companies, and by 2001 this numbers had increased to 41%<sup>77</sup>. Indeed, most of these sponsors are small or medium-size companies that pop up into the market precisely because of the public incentives of the Orphan Drug legislation.

A major second indirect effect of the orphan drug incentives is the introduction into the market of certain medicinal products designed for rare diseases but also working on some other common ailments. For instance, the controversial human growth hormone (hGH)<sup>78</sup> developed by Genentech to treat an specific

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<sup>72</sup>These data were drawn from the FDA web page at <<http://www.fda.gov/orphan/designat/list.htm>> (last accessed: March 1<sup>st</sup> 2004).

<sup>73</sup>Milne et al., *supra* note 11, at 11.

<sup>74</sup>Haffner, *supra* note 28, at 40.

<sup>75</sup>For a somehow critical view on the Orphan Drug Act and its alleged uncertainty under the producers' perspective, cf. Robert A. Bohrer & John T. Prince, *A Tale of Two Proteins: The FDA's Uncertain Interpretation of the Orphan Drug Act*, 12 Harv. J.L. & Tech. 365, 379-383.

<sup>76</sup>Milne et al., *supra* note 11, at 8-9.

<sup>77</sup>Maeder, *supra* note 1, at 84-85, citing an study by the Tufts Center for the Study of Drug Development.

<sup>78</sup>The human growth hormone is one of the most cited examples of the so-called "orphan blockbusters", that is, orphan drugs that have generated huge benefits for its sponsors, therefore calling into question the soundness of their designation. Cf. Subsection 4.1.



growth disorder on children, hypopituitary dwarfism, has proven to be also effective in treating other growth problems<sup>79</sup>.

The overwhelmingly optimistic assessment of orphan drug legislation is also present on the other side of the ocean. Despite the short period of implementation of the European legal framework, almost four years<sup>80</sup>, the considerable amount of work EMEA and COMP have had to tackle during this period is a good indicator of initial success of the EU policy on the field of orphan medicinal products. Today, the number of designated products is 185, according to the Community Register of Orphan Medicinal Products for Human Use<sup>81</sup>. Close to 250 applications had been received by April 2003 (two-thirds successful), and 32 marketing authorizations had been requested by then, of which 8 resulted in a marketing authorization<sup>82</sup>. Even though the data on final availability to the patients are still scarce, authorized voices have expressed their satisfaction with how the system is working<sup>83</sup>.

All active substances approved to be marketed in the US by the FDA were reviewed by the Community authorities in order to determine the possible pre-existence of a marketing authorization in the EU territory even before orphan status became available. The results revealed that 85% of orphan products available in the United States due to the incentives offered by the orphan drugs had also been marketed within the Community via either the EU centralized procedure or, in most cases, the national authorities and the mutual recognition system<sup>84</sup>. Indeed, up to five applications for marketing authorization through the centralized procedure were withdrawn during the evaluation phase. Nevertheless, these numbers may be misleading: only a quarter of the products subject to mutual recognition have received market authorization in *all* of the 15 member states, and thus the orphan medicinal products available in practice to all EU patients amount approximately to 50% of the total number of drugs from which their American counterparts benefit<sup>85</sup>. Therefore, the orphan drug laws in Europe have a long way to go, even if some progress had been made

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<sup>79</sup>Bohrer & Prince, *supra* note 75, at 381.

<sup>80</sup>The first appointed COMP began to work in April 17<sup>th</sup> 2000. EMEA Report, *supra* note 59, at 2.

<sup>81</sup>*Cf.* <<http://pharmacos.eudra.org/F2/register/orphreg.htm>> (last accessed: March 1<sup>st</sup> 2004). EMEA regularly publishes press releases informing about the results of the monthly meetings of the COMP, including all the designations made in each period. These documents may be found at the Agency's web page, <<http://www.emea.eu.int/index/indexh1.htm>>.

<sup>82</sup>EMEA Report, *supra* note 59, at 2. As of January 2004, 12 orphan medicinal products have been awarded a marketing authorization. *Cf. supra* note 81.

<sup>83</sup>*Cf.*, for instance, the words of Mrs. Grossetête, Rapporteur for the Regulation on Orphan Medicinal Products at the European Parliament, and Mr. Torrent-Farnell, Head of the COMP in *Id.* at 9-10. However, as the very Report points out "[...] in spite of these encouraging results, it is yet to early to estimate what percentage of the designated medicines will eventually receive a market authorization". *Id.* at 11.

<sup>84</sup>*Id.* at 35.

<sup>85</sup>*Id.* at 35.

before they came into force.

Similarly, the EU orphan drug laws are considered to have a special impact on the biotechnological industry and small and medium-sized companies with a limited portfolio of products<sup>86</sup>. However, assessing the effects of orphan drug regulations on R&D activities and the development of the European industry generally seems to be a pending task. Yet, the biotech sector in Europe has grown considerably during the last decade, and this trend became accentuated in the period 2000-2001 (first year of implementation of the European orphan drug regulations), where the biopharmaceutical R&D expenditure shifted from Ä4,977 million to Ä8,354<sup>87</sup>. Despite these encouraging results, again it seems that Europe has a lot of work to do in order to catch up with its American competitor (Ä17,522 in 2001)<sup>88</sup>.

In conclusion, the empirical data point out that the orphan drug policies have proved to be an important boost for the treatment of rare diseases and, more generally, for the economic and scientific development of the pharmaceutical industry. However, it is necessary to avoid any and all forms of self indulgence. Since the initial steps of such policies in the US during the early 80s, sharp attacks have arisen from many sectors criticizing certain points embodied in the Orphan Drug Act and its ancillary regulations. These viewpoints have been reflected in the many attempts for reform that have taken place and also in the passage of the European legal architecture. A good global assessment of the American orphan drug policy, consistent with the thesis proposed in this paper, was made in 1995:

“The cumulative effect of these provisions is that the Orphan Drug Act has been a clear, although not unqualified success. Only ten orphan drugs had reached the market in the ten years prior to its enactment. Comparatively, in the ten years following passage of the Act, eighty-seven orphans reached commercialization. [...]In 1990, PMA member companies spent \$543 million on orphan drug research. Thus, the evidence indicates that the Act has succeeded in stimulating substantial commercial investment”<sup>89</sup>.

In conclusion, there is empirical data which points to both an overwhelmingly positive evaluation of the American long-standing experience and a hopeful kick off for the recently-born European initiative. However,

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<sup>86</sup>Small and medium enterprises represent two-thirds of the total number of sponsors. Id. at 18.

<sup>87</sup>Data drawn from the web page of “Emerging Biopharmaceutical Enterprises”, an organization representing the biopharmaceutical industry in Europe, at <<http://www.ebe-efpia.org/biotech.htm>>.

<sup>88</sup>Id.

<sup>89</sup>Janice Marchiafava Hogan, *Revamping the Orphan Drug Act: Potential Impact on the World Pharmaceutical Market*, 26 Law & Pol’y Int’l Bus. 523, 530 (1995).

it may not be denied that there is a widespread feeling that present provisions can be ameliorated to correct some of the deficiencies detected throughout the last twenty years, curbing some stunning abuses, clarifying a few obscure provisions and providing solutions for some challenges which have not been paid enough attention to.

#### 4.

### Addressing Critiques. Main Concerns in Light of the American Experience and their Responses in the European legislation.

Despite the widely-shared positive assessment on the role played by Orphan Drug regulations towards a greater availability of this category of drugs, even during the Congressional hearings that preceded the Orphan Drug Act of 1983 and repeatedly since then many voices criticizing some points of the letter of the law and several of its practical outcomes have been heard. The myriad of Congressional attempts for reform that have been taking place since 1983, whether successful or not, are direct evidence of this dissatisfaction. Pharmaceutical manufacturers have insisted on the argument that the Act does not provide the degree of certainty required to achieve its full potential for innovation (e.g. about the definition of “sameness” as applied to competing products)<sup>90</sup>. On the other side of the arena, patients and their advocates sharply criticize the effect of the Orphan Drug Act on prices and industry profits<sup>91</sup>.

This Section will discuss the most notorious points of controversy. Indeed, there are other issues raised by interested parties and scholars<sup>92</sup>, but this paper will concentrate only on those which have been object of serious public debate and which had some impact in Europe when the 2000 Regulations were enacted. The purpose is to scrutinize each criticism and its repercussion in the United States, analyzing the normative solutions that have been proposed, and finally, to take note of what European authorities have done.

#### 4.1.

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<sup>90</sup>Clissold, *supra* note 10, at 131.

<sup>91</sup>*Id.* at 131.

<sup>92</sup>A good example of the latter is the purported unconstitutionality of the Orphan Drug Act asserted by John Flynn. *Cf.* generally John Flynn, *The Orphan Drug Act: an Unconstitutional Exercise of the Patent Power* 1992 Utah L. Rev. 389 (1992). This author maintains that Congress is not constitutionally empowered to grant a patent-like right, evading in an irregular manner the patent clause embodied in the US Constitution, so long as many of the protected orphan drugs are already known to be effective and may not qualify as “discoveries”, as required by such clause. Other commentators claim that alternative, constitutionally-consistent interpretations are possible. *Cf.* Pulsinelli, *supra* note 5, at 338-339.

### The Risk of Abuse: Orphan Blockbusters.

Without a doubt, the largest concern by far that commentators and legislators have detected in the American orphan drug regulatory framework arises from the factual evidence that some medicinal products designated as “orphans” and therefore benefiting from the incentives embodied in the orphan drug laws (most notably, from market exclusivity rights), have produced such enormous benefits for their sponsors that they have called into question their own status as orphan drugs and the entire legal architecture<sup>93</sup>. These drugs fulfilled all the statutory requirements under the Orphan Drug Act, obtained a designation and subsequently a marketing authorization; but their sponsors have reaped considerable benefits in some cases recovering the development costs in the first couple of years since initial access to the market. Think for example on orphan drugs that must be administered to chronic patients during a prolonged lapse of time or even their entire lives, or on remedies for infectious ailments that are spreading rapidly.

The influence of market exclusivity rights on the existence of these “blockbuster drugs” is evident: the 7-period protection curbs any actual or potential competition for the designated drug, enabling the sponsor to charge monopoly prices for the drug. However, it must be noted that this is precisely the very intent of the Act: to offer a monopolistic position to encourage the industry to develop products that would not be otherwise manufactured<sup>94</sup>. Therefore, these cases can be defined as “abuses” of the actual statutory protection, as situations where the letter of the law goes beyond its purpose by affording protection to orphans that already have parents willing to take care of them. A good example, cited by many authors, is Ceredase, a remedy for Glaucher’s disease, which afflicts around 2,000 Americans<sup>95</sup>. Genzyme, the biotech sponsor has been accused of taking advantage of the monopoly position in the US under the orphan drug legislation to earn close to half a billion dollars a year by charging patients between \$100,000 and \$400,000 annually for their treatment, depending on whether the person is a child or an adult<sup>96</sup>.

The core objective here is striking a balance between encouraging innovation and avoiding monopoly prices during the temporary protection afforded by market exclusivity rights. Some have argued that this is an

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<sup>93</sup>Pulsinelli states that “the commentary all focuses on essentially the same four or five drugs: AZT(HIV infection/AIDS); pentamidine isethionate (pneumonia associated with AIDS); human growth hormone (hGH) (improper growth in children lacking the enzyme), erythropoietin (EPO) (anemia associated with end-stage renal disease); and Ceredase TM (Glaucher’s disease)”. Pulsinelli, *supra* note 5, at 316-317.

<sup>94</sup>*Id.* at 318.

<sup>95</sup>Maeder, *supra* note 1, at 85-86.

<sup>96</sup>*Id.* at 86. Maeder talks about Ceredase as the “world’s most expensive medicine”.

“all or nothing” debate, a flat choice between having expensive drugs or not having them at all and therefore letting patients down<sup>97</sup>. However, the problem happens to be a little more complex, as the many attempts for statutory reform specifically addressing this issue plainly show; and today there exists a wide-spread consensus favoring a legislative reform that may curb these scarce (about 10% of the total number of orphan drugs approach this blockbuster status<sup>98</sup>) but nevertheless disturbing abuses.

A main second problem associated with the phenomenon of profitable orphans is the situation of firms racing each other for obtaining designation and thus a monopoly position in the market. Pulsinelli has detected two main difficulties arising from this observable fact. First, the very idea of a race questions the “orphan status” of these products, provided that “true orphans” hardly ever may attract the attention of more than one parent. As Pulsinelli puts it, “the fact that firms are fighting over these drugs suggests that in fact they are likely to be profitable, and hence it is an abuse of the orphan drug incentives if they are applied to these drugs”<sup>99</sup>. Second, such a race does not produce anything but a waste of resources, specially on the part of the loser, since its investment will not receive any sort of reward<sup>100</sup>.

But the so-called “orphan blockbuster” is not only explained by the monopoly conferred by market exclusivity. Experts have also pointed to “expanding orphan diseases” as the other leading cause of profitable orphan drugs<sup>101</sup>, that is, to indications that affect less than 200,000 people in the US at the time the drug is designated, but that later on surpass that population. Undoubtedly, the paradigm here is AIDS. Many of the initial remedies for HIV infection and the diseases related to it were awarded protection under the orphan drug law, but have subsequently happened to be extremely profitable, as the infection has spread out and the potential market has grown<sup>102</sup>. Full-blown AIDS surpassed the 200,000 patients cap in 1993 and many of the opportunistic diseases can no longer be considered for orphan designation<sup>103</sup>, but the same problem might arise with any other illness. In other cases, orphan drugs have become blockbusters through their use for off-label indications, i.e. indications other than those studied under the clinical trials and laid down in

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<sup>97</sup>Pulsinelli, *supra* note 5, at 318-319.

<sup>98</sup>Sheila R. Schulman et al., *Implementation of the Orphan Drug Act: 1983-1991*, 47 Food & Drug L.J. 363, 402 (1992).

<sup>99</sup>Pulsinelli, *supra* note 5, at 320.

<sup>100</sup>*Id.* at 321. This second problem

<sup>101</sup>*Id.* at 323. *Cf.* also Clissold, *supra* note 10, at 133-134.

<sup>102</sup>AZT is probably the best example of this kind of profitable orphans. AZT is part of the initial treatments against full-blown AIDS, when this ailment broke out. AZT was awarded marketing approval in 1989 for the treatment of an estimated population of 45,000 people. Shortly after, it was demonstrated that the drug also was effective for delaying the appearance of full-blown AIDS, and therefore the potential number of users was increased by the 600,000 asymptomatic HIV carriers existing at that time. David D. Rohde, *The Orphan Drug Act: an Engine of Innovation? At What Cost?* 55 Food & Drug L.J. 125, 135 (2000)

<sup>103</sup>Pulsinelli, *supra* note 5, at 323.

the FDA approval<sup>104</sup>. This phenomenon occurs because physicians are authorized under their discretion to prescribe medicines for conditions not included in the label of the product, therefore expanding the possible uses of the particular drug and, as a consequence, also its profit margins<sup>105</sup>.

Once the problem of blockbuster drugs has been described, it is time to examine the actual and prospective solutions that may address it<sup>106</sup>. It must be noted that several amendments to the Orphan Drug Act can well be explained by the overwhelming concerns with the above-mentioned abuses, and that none of these reforms achieved significant success.

The first of the initiatives that have been proposed to curb abuses, and perhaps the most popular, is the so called “shared exclusivity.” This proposal was underlying the reform initiatives presented in 1986, 1987 and 1990<sup>107</sup>, and it basically consists on an authorization for sharing market exclusivity between two or more sponsors that have developed their products “simultaneously,” i.e., during an approximately coincident period of time. Obviously, this sort of proposals have been strongly opposed by the industry, since successful companies would be forced to divide up the benefits reaped once the products are on the market, and that allegedly would disturb the initial financial risk assessment that producers make when deciding whether to begin to develop a drug or not<sup>108</sup>. However, cross-licensing agreements, joint ventures and other sorts of collaborative schemes have been used by industry members to minimize the risk of the investment<sup>109</sup>. In

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<sup>104</sup>Clissold, *supra* note 10, at 134-135.

<sup>105</sup>Pulsinelli does not share the kinds of concerns pertaining to the off-label use of orphan drugs. He argues that off-label use does in fact increase competition, and that if the off-label market is attractive enough, other companies would seek approval for drugs specifically addressing these indications. Pulsinelli, *supra* note 5, at 339-340.

<sup>106</sup>As for the actual solutions, the supporters of the actual version of the Orphan Drug Act (mainly the industry) tend to cite the formal or informal programs put in place by most pharmaceutical and biotechnological companies for providing indigent patients with free drugs and the parallel public initiatives on the field. Maeder, *supra* note 1, at 86-87. However, even accepting the statement that no one with a rare disease has been unable to obtain a designated orphan drug because of financial causes, this does not solve the root of the problem: that some companies are reaping huge benefits in part due to the abuse from a protective legislation, and that final consumers are paying artificially high prices.

<sup>107</sup>In 1986, the concept of shared exclusivity was introduced for the first time in a reform proposal to allow sharing exclusivity rights among drugs that were developed “simultaneously”. The proposal introduced in 1987 was limited to generic drugs. In 1990, the final version of the amendment established some more strict requirements to define “simultaneous” development through different types of time limits in order to assure that the development of the product was in fact “simultaneous”. However, as it was mentioned, the 1990 Amendment was pocket-vetoed by President George H. Bush. The Orphan Drug Amendment of 1994 reintroduced the same provisions of its predecessor, but Congress did not approve the initiative.

<sup>108</sup>Pulsinelli, *supra* note 5, at 329. Pulsinelli generally aligns with the industry positions and rejects the introduction of shared exclusivity concluding that “[...] while a change in the Orphan Drug Act to allow shared exclusivity might enhance cooperation and seem more ‘fair’ to losers, the severe damage to the Act’s incentives and the enormously increased administration costs weigh against enacting such change”. Pulsinelli, *supra* note 5, at 331.

<sup>109</sup>Clissold, *supra* note 10, at 134-135. Clissold cites a study by Schulman (*cf. supra* note 98) which describes that 69 joint ventures or licensing agreements have taken place recently, even though 83% of orphan products remain to be sponsored by a single company.

fact, joint efforts seem to be a good option for supporting innovation in the field of orphan drugs, since they would help to solve some of the structural difficulties that sponsors face when dealing with orphan drugs (limited patient population and the like), thus increasing efficiency all across the industry<sup>110</sup>.

The second main initiative proposed in the United States has been the reduction of the market exclusivity term<sup>111</sup>. Actually, this period is seven years, but some proposals for statutory amendments have tried to abbreviate this period substantially. For instance, the 1992 Amendments established a sales cap of \$200 million. The exclusivity right was awarded for two years and after that time and over the next seven years, the exclusivity term could be revoked if the sales threshold was surpassed. In a parallel fashion, the 1994 Amendments put forward a new period of four years, extendable for three extra years if the sponsor was able to show that it was a drug of “limited commercial potential”<sup>112</sup>. The problems that commentators have found with these limitations are analogous to those arising from the initial version of the statute, which asked producers to provide certain sensitive and often unverifiable data<sup>113</sup>. However, note that the data here refer to the past (actual sales volume) and not to the future (expected benefits).

The third recognized initiative that should be examined is the revocation of exclusivity rights once a generating event takes place. In normal conditions, this “event” is the achievement of a certain level of sales or profits, and normally the former option is preferred, so long as sales numbers are more easy to ascertain and less awkward for the industry<sup>114</sup>. On the other hand, they are also “much less accurate”<sup>115</sup>, since the development costs and other factors influencing the final result from an investment vary widely across the industry. Nevertheless, the 1992 Amendments followed the path of establishing a sales level of \$200 million as the situation that would automatically lead to a revocation of the exclusivity status. An alternative for this “trigger” event is an increase in the number of patients that surpasses the cap of 200,000 Americans, and this was the option taken by the 1990 Amendments<sup>116</sup>. From all the solutions to address the issue of orphan profitability, revocation of exclusive marketing rights appears to be the one with a wider consensus in its support<sup>117</sup>, so long as it is perhaps the less aggressive initiative and the one that happens to respect the

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<sup>110</sup>*Id.* at 145.

<sup>111</sup>Pulsinelli, *supra* note 5, at 332.

<sup>112</sup>*Cf.* 140 Cong. Rec. S3684, S3728 (daily ed. March 24, 1994) (statement of Senator Kassebaum discussing the provisions of the Orphan Drug Act Amendments of 1994).

<sup>113</sup>Pulsinelli, *supra* note 5, at 333.

<sup>114</sup>*Id.* at 333-334.

<sup>115</sup>*Id.* at 334.

<sup>116</sup>*Id.* at 334-335.

<sup>117</sup>Even Pulsinelli acknowledges that “these provisions seem to be reasonable enough”. *Id.* at 335. The National Organization

initial structure of incentives to a higher degree. In any event, the bright-line rule based on the prevalence of the disease is called into question and suffers criticism for being an inadequate proxy for unprofitability. Revocation appears then as a sound mechanism for relaxing the rule and bringing it closer to reality.

Fourth and last, authors tend to mention among the measures that have been often proposed during the 20 years of orphan drug regulatory experience in the United States the creation of a windfall profit tax on all profits accruing from the marketing of orphan drugs above a given threshold<sup>118</sup>. Through different versions, the same scheme has been presented in Congress in 1990, 1991 and 1993 by Representative Stark from California<sup>119</sup>. The main idea is to tax benefits from an amount of revenues equal to the production costs plus, in some cases, a certain volume. Again, the main alleged pitfall of the proposal is the disclosure obligations that imposes to the industry<sup>120</sup>; but it seems hard to distinguish these duties from other imposed under various other tax laws.

From what was described so far, one conclusion appears to be clear: it is necessary to strike a new balance between innovation encouragement and industry profit and pricing, between incentives and competition. Both over- and underprotection are equally bad for patients and society as a whole, which should be the primary beneficiaries of the law. Even though the cases of abuse are not numerous, action should be taken to address this particular issue amending the Orphan Drug Act to include some of the measures described above. In particular, the revocation mechanism may be a very useful tool to curb abuse by the industry, and this is what the European legislators seem to have had in mind when they enacted Regulation 141/2000.

In the European Union, the concern about possible abusive practices by the industry was present since the initial steps of the EU orphan medicinal product legislation<sup>121</sup>, and this concern was echoed in some provisions of the Regulation 1441/2000 cited above. First, the Regulation finally chose an epidemiological criterion to define the concept of “orphan drug”, by setting up a prevalence ratio of less than 5/10,000 people, lower than the one established in the US (approximately 7.5/10,000). Thus, the same controversy that has taken place in the United States about the accurateness of a bright rule as a proxy for nonprofitability are

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for Rare Disorders (NORD) has clearly expressed its support to a rule like these. Veronica Henry, *Problems with Pharmaceutical Regulation in the United States* 14 J. Legal Med. 617, 636 (1993).

<sup>118</sup>Pulsinelli, *supra* note 5, at 335-336.

<sup>119</sup>*Id.* at 336.

<sup>120</sup>*Id.* at 336.

<sup>121</sup>For instance, the Presentation of the initial Proposal of Regulation (*cf.* note 40) acknowledges that “some of the medicinal products designated as orphan drugs in the United States have subsequently proved to be (extremely) profitable”.



likely to occur in Europe. However, this numerical cap is combined with a more flexible economic test: an orphan medicinal product may also be designated as such provided the sponsor can show that, without the incentives provided by this status, development of these medicinal products would not be undertaken. In sum, the designation criteria open the door to exactly the same source of problems as the US system witnessed.

As for the duration of the exclusivity privilege, European regulators chose a longer term (10 years, versus 7 in the US), but also included a revocation clause in Article 8 of the Regulation. Under that provision, the exclusivity period may be reduced to 6 years in the event that, at the end of the fifth year it is established that the designation criteria (i.e. nonprofitability, prevalence of the disease) are no longer met. Consequently, EU law has been clearly influenced by the various proposals presented in the US favoring the limitation of the market exclusivity benefit in certain cases<sup>122</sup>. In any event, this progress may be offset by the longer duration of the legal monopoly, and it is still too early to figure out how it is going to work in practice (will companies be required to provide COMP or EMEA with data?). So far, the Communication from the Commission on Regulation 141/2000 vaguely states that “the Commission will put in place the necessary procedures and systems in order to monitor the prices of orphan medicinal products [...]”, as well as profitability<sup>123</sup>. The Communication also recommends that at the end of the fifth year of market exclusivity the competent authorities “systematically check whether or not the criteria on which basis market exclusivity was granted are no longer met”<sup>124</sup>.

As for what was termed above “shared exclusivity”, the EU law has not included any similar provision to those included in the various unsuccessful Amendments to the US Orphan Drug Law. The wording of article 8.1 of the Regulation is straightforward: neither the Community nor the Member States shall “[...] grant a marketing authorization for the same therapeutic indication in respect of a similar medicinal product” unless any of the derogations set out in article 8.3 apply<sup>125</sup>. Therefore, after one of the products receives marketing authorization by either procedure, in most cases other applications will be refused unless the new

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<sup>122</sup>Furthermore, in Article 5.12 of the Regulation 141/2000 it is provided a cause of removal from the Community Register of Orphan Medicinal Products that refers to the fact that “the criteria laid down in Article 3 [designation criteria] are no longer met in respect of the medicinal product concerned”. This clause may be characterize as a sort of market exclusivity revocation even before this period starts, or as a reevaluation by the COMP of the designation requisites.

<sup>123</sup>Communication from the Commission on Regulation (EC) no.141/2000 on orphan medicinal products, *supra* note 49, at 10.

<sup>124</sup>*Id.* at 10.

<sup>125</sup>Article 8.3 embodies the following situations: a) consent of the initial sponsor, b) initial sponsor unable to supply sufficient quantities to meet the demand, and c) clinical superiority.

applicants may prove that the second product is safer, more effective or “otherwise clinically superior”, in parallel to what happens in the US. This issue will be revisited in Subsection 4.2.

Finally, the alternative of the windfall profit tax was not even considered under the EU regulations, due to the fact that, as we described in Section 3, the Community is barred from establishing any tax system under the current versions of the Treaties. Again, this topic will be considered in Subsection 4.7 when referring to some particular features and limitations of the European legal framework.

As a brief conclusion, the European orphan drug law has made some progress in light of the experience gained in the US during the last 20 years and the criticisms raised in this country. However, the innovation has not been substantial and how the revocation clause will be applied by the Community authorities remains uncertain. Therefore, some of the debates that are actually going on in the US are likely to be echoed on the other side of the Atlantic in the near future.

#### 4.2.

### Clarifying Ambiguities: the “Same Versus Different” and “Clinical Superiority” Problems.

The second of the main problems revealed by the American experience with the regulation of orphan drugs consists of the ambiguities that the Orphan Drug Act presents in defining the boundaries of the market exclusivity protection. This issue was traditionally termed as the “same versus different” problem<sup>126</sup>. Initially, neither the Act nor other regulations encompassed any provision establishing when a posterior drug was the “same” as the pioneer drug and hence barred from being introduced into the market to compete with the initial remedy<sup>127</sup>. Once a designated orphan drug was awarded marketing approval, all “same” medicinal products were not eligible to be commercialized. However, the lack of definition for “sameness” lead to important controversies, among which the case of the human growth hormone (hGH) is frequently cited as an illustration by commentators<sup>128</sup>. Genentech Inc. had developed Protropin, a recombinant human growth hormone to treat the deficiency of such hormones, receiving marketing authorization by the FDA in

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<sup>126</sup>For a detailed study addressing this topic more deeply than the aim of this essay intends to do, *cf.* generally, Bohrer & Prince, *supra* note 75.

<sup>127</sup>Clissold, *supra* note 10, at 131.

<sup>128</sup>*Cf.* for instance, Rohde, *supra* note 19, at 133-134.

October 1985<sup>129</sup>. Subsequently, Eli Lilly & Co. requested approval for introducing its own hGH product, Humatrope, in the market in June 1986. Genentech went to the court seeking temporary injunctive relief to prevent its competitor from getting FDA approval, claiming that Humatrope was the “same product” as Protropin. The District Court refused to decide the case, setting no general rule for determining when two drugs must be considered to be the “same” product or “different” ones under the Orphan Drug Act, and instead declared that such duty is statutorily imposed on the FDA<sup>130</sup>. However, FDA subsequently granted marketing approval for Humatrope, and from that moment and until the 1993 Regulations, has decided this type of incidents on a case-by-case basis.

The remedy to the lack of legal standards came with the 1993 Regulations. The final option adopted by FDA was based on the so-called “structural similarity” criterion, distinguishing between macro- and micromolecular drugs. For the former, if both compounds have only “minor” differences in aminoacid sequence, there are considered to be the same product<sup>131</sup>. The latter drugs are presumed to be the same if the “active moiety” is identical between both<sup>132</sup>. In both cases, the presumption can be rebutted if the second sponsor effectively demonstrates that its orphan is “clinically superior”, which entitles the drug to receive marketing authorization as well. The definitions laid down in the Regulations refer to “clinical superiority” as the situation where “a drug is shown to provide a significant therapeutic advantage over and above that provided by an approved orphan drug (...)”. This advantage may consist on greater effectiveness, higher levels of safety or any other “major contribution to patient care”<sup>133</sup>, and the burden of proving it is borne by the second sponsor<sup>134</sup>. The “same versus different” problem was therefore at least partially solved by the significant certainty added to the statutory framework by the FDA regulations and the risk of “free riding” (purportedly caused by one firm introducing cosmetic changes in the structure of a previously marketed drug and claiming that the new compound is a “different” one) was ruled out as well<sup>135</sup>. However, a recent

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<sup>129</sup>Clissold, *supra* note 10, at 131-132.

<sup>130</sup>*Id.* at 132. The case reference is *Genentech Inc. v. Bowen*, 676 F. Supp. 301 (D.D.C. 1987).

<sup>131</sup>*Id.* at 137. Large molecular drugs tend to be biotechnological products.

<sup>132</sup>“Active moiety” is defined in §316.3(b)(2) of the Regulations as “the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (...), or other noncovalent derivative (...) of the molecule, responsible for the physiological or pharmacological action of the drug substance”.

<sup>133</sup>§316.3(b)(3) of the 1993 Regulations. The expression “major contribution to patient care” must be understood narrowly, and the other variables are easily ascertainable through comparing clinical trials. Haffner, *Orphan Products, Ten Years Later and Then Some* 49 Food & Drug L.J. 593, 599 (1994). The only example given by the FDA as a “major contribution to patient care” was the development of an oral dosage where only a parenteral option had been available previously. Joseph A. Levitt & John V. Kelsey, *The Orphan Drug Regulations and Related Issues*, 48 Food & Drug L.J. 525, 529 (1993).

<sup>134</sup>Some commentators have posed the question of whether a lower price might qualify as a “major contribution to patient care”, but this idea deserves immediate rejection, since considerations about prices fall well beyond the mandate of the FDA *Id.* at 528.

<sup>135</sup>However, Pulsinelli mentions a recent case; *Berlex Lab. Inc. v. FDA*, 942 F. Supp. 19 (D.D.C. 1996), where the application

publication criticized the fact that “the standards used [in the US] to judge superiority are less than clear”, leaving the agency with too much discretion to make such finding<sup>136</sup>.

The marketing exclusivity rights that any orphan drug enjoys may therefore only be disturbed by an identical product (defined in terms of their composition) if the latter triggers some kind of benefit that the former lacked. The approach taken in Europe resembles this model substantially. As described above, article 8.3(c) of the Regulation 141/2000 makes an exception to market exclusivity when a second similar medicinal product may be shown to be “safer, more effective or otherwise clinically superior”. The parallelism with the FDA Regulations is obvious. The concepts of “similar medicinal product” and “clinical superiority” are detailed by Regulation 847/2000, which encompasses definitions strikingly similar to those of the American orphan drug law. “Similarity” is defined by the existence of a “similar active substance”<sup>137</sup> in both products, that is, “an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of the same molecular structural features) and which acts via the same mechanism”, according to the relevant statutory provisions<sup>138</sup>. The imitation of the wording of its American counterpart continues when Regulation 847/2000 addresses the characterization of clinical superiority. As article 8.3(d) provides, a medicinal product is clinically superior when it offers “a significant therapeutic or diagnostic advantage over and above that provided by an authorized orphan medicinal product”, i.e., greater efficiency, greater safety or any other “major contribution to diagnosis or to patient care”<sup>139</sup>. In sum, if there is an area in which the European orphan drug law can be deemed as a mere copy of its American elder brother, it will be that involving the so called “similar versus different” problem. Therefore, the same issues of vagueness described above apply in both jurisdictions, although great progress was made when the 1993 FDA Regulations were issued.

#### 4.3.

of the notion of “clinical superiority” by the Agency lead to litigation challenging it. The Court upheld the FDA position on the merits after using a very deferential standard for reviewing this type of decisions.

<sup>136</sup>Brian Reid, *New Products Highlight Ambiguity of Orphan Drug Law* 21 *Nature Biotechnology* 6, 6-7 (2003). The example used by the author is the struggle between Fabrazyme (from Genzyme General) and Replagal (from Transkaryotic Therapies), two drugs designed to treat Fabry disease, a lethal and uncommon liposomal storage disorder.

<sup>137</sup>“Active substance” must be understood to mean “a substance with physiological or pharmacological activity”, according to Article 3.3(a) of the Regulation 847/2000.

<sup>138</sup>Article 3.3(c) of the Regulation 847/2000. These provision also contains specific, explanatory examples of similar active substances.

<sup>139</sup>This third way of clinical superiority applies only, as the text of the article makes clear, “in exceptional cases”. The meaning of this wording is obviously far from clear.

### Salami Slicing: “Creative” Subsets and their Remedy.

The term “salami slicing” refers to the practice used by many applicants trying to define one stage or manifestation of a particular disease as a differentiated condition entitled to protection under the orphan drug laws so long as the designation criteria (most significantly, the prevalence threshold) are met<sup>140</sup>. This sort of “trick” takes advantage from the fact that the FDA permits sponsors to parse diseases into “medically plausible subsets”<sup>141</sup>, and often involves complicated debates within the scientific community over terminology and the bounds of medical definitions. Through this tool, companies could obtain market exclusivity and all the other statutory benefits and incentives for multiple indications that together may exceed 200,000 people, getting rid of the bright-line rule based on prevalence.

The “salami slicing” problem was specifically addressed by the 1993 Regulations<sup>142</sup>. Under these norms, the Office of Orphan Products Development (OPD) at the FDA must examine each orphan drug application in order to make clear that the declared patient population is not an “arbitrary subset” of the actual number of people afflicted by the disease at the time the request for designation is made. The test laid down in §316.21(b) of the Regulations is based on the concept of “medical plausibility”: any targeted population that happens to be medically implausible would be automatically considered as an “arbitrary subset” of the real condition and the application would be rejected on these grounds<sup>143</sup>. For instance, using the example put forward by Haffner, “arbitrarily defining end-stage cancer as a subgroup would not be acceptable if the drug can be used in a broader cross-section of patients”<sup>144</sup>.

The OPD has outlined a set of principles to be applied when assessing patient population claims under the “medical plausibility” standard. Hence, the OPD will consider the basic pathologic process as the condition entity, unless there are special circumstances playing against this rule (location, age group or special regulatory requirements), and chronic diseases that evolve with time will be deemed to be the same ailment for designation purposes<sup>145</sup>. It must be noted that even Marlene Haffner (Director of the OPD) acknowledges that “any system used to define ‘medically plausible’ will appear subjective to some observers, since the

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<sup>140</sup>Maeder, *supra* note 1, at 87. This arbitrary subdivision is very common in cases involving cancer, where companies try to pick the rarest subcategory they can figure out in order to meet the 200,000 patient population requirement. Margolis, *supra* note 1, at 21.

<sup>141</sup>Maeder, *supra* note 1 at 87.

<sup>142</sup>*Cf. supra* note 25.

<sup>143</sup>Clissold, *supra* note 10, at 137.

<sup>144</sup>Haffner, *supra* note 133, at 596.

<sup>145</sup>*Id.* at 597.

process is not clearly defined by law”<sup>146</sup>. However, this situation can be considered to be unavoidable, since the distinctions on the boundaries may be blurred and indeed there may exist scientific controversy on how to define a particular disease or condition. Notwithstanding, regulators should try to set up clear and unambiguous rules that at the same time may promote certainty and contribute to curb any abuse by industry. Both the 1993 Regulations in the United States and the EU Commission Regulation 847/2000 point in this direction.

In the European Union, the Regulation 141/2000 deferred the implementation of the designation criteria laid down in article 3.1 to the subsequent Commission Regulation 847/2000, which in turn establishes specific rules to assure that the prevalence claims are accurate and in check with reality. Article 2 of Regulation 847/2000 forces sponsors to provide documentation that include “appended authoritative references which demonstrate that the disease or condition for which the medicinal product would be administered, affects not more than five in 10,000 persons in the Community at the time at which the application for designation is submitted, where these are available”. The text continues requiring that such documentation must encompass or refer to “relevant scientific literature” and “relevant databases” existing in the Community or third countries. This wording may be interpreted to call for sufficient explanation of the medical plausibility of the patient population targeted, and of course COMP will exert a complete review of the application, obviously including the rightfulness of the disease definition. The EMEA Report cited in Chapter 3.3<sup>147</sup> mentions a document produced by COMP entitled “Points to Consider on the Calculation and Reporting of Prevalence of a Condition for Orphan Designation”, where the issue of preventing “salami slicing” is addressed. However, the EMEA Report itself recommends a deeper definition of what would constitute a “valid subset” “with valid and unambiguous examples that may help sponsors to prepare their applications and bring more objectivity into the procedure<sup>148</sup>.”

#### 4.4.

### **High Prices: the Undesired Effects of Monopoly on Reimbursement Policies.**

The pricing problem described in Subsection 4.1. has immediate repercussions on the cost of public and

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<sup>146</sup>*Id.* at 597-598.

<sup>147</sup>EMEA Report, *supra* note 59, at 22-23.

<sup>148</sup>*Id.* at 23.

private health care systems all over the world. Since the actual letter of the law does not effectively curb any abuse by companies, high prices severely harm families that lack health insurance or that have lower lifetime caps or unaffordably high premiums in their plans<sup>149</sup>. Besides, the problem concerns public budgetary appropriations in public health coverage programs such as Medicare and Medicaid in the US or other more extensive Social Security systems, like those operating in most of the EU members. For instance, Medicare spent only in Epogen under its renal dialysis program around \$100 million in 1990<sup>150</sup>. Also countries with price controls over medicinal products (almost all western countries with the only exception of the United States), face serious challenges as a consequence of highly-priced drugs, since their negotiation position is seriously compromised by having to deal with a legal monopoly<sup>151</sup>.

Apart from the initiatives devised to avoid excessively profitable orphans, described above, this problem is only part of the more general pharmaceutical cost dilemma, and must be solved by legislatures and governments beyond the bounds of specific orphan drug regulations<sup>152</sup>. Neither FDA nor EMEA have any authority over price control. However, some modest contributions can be made from the orphan drug field. NORD, for instance, proposed, among a variety of cost-containment measures, establishing a separate fund under Medicare to finance purchase of orphan drugs and mandating the currently voluntary free drug giveaway programs of pharmaceutical manufacturers<sup>153</sup>. However, it should be kept in mind that the very purpose of the US Orphan Drug Act and its market incentives is antithetical with any attempt to control drug prices. This causes two main dilemmas. First, countries which implement pricing control over medicines are free riding those which try to promote development by providing, among other incentives, monopoly profits. This could have been the case of the US, which, as some commentators argue, bears the overwhelming majority of the drug development costs worldwide because of the lack of government-imposed price caps<sup>154</sup>. Second, jurisdictions such as the EU, where both schemes (orphan drug incentives and price limitations) are put in place might face a deep contradiction, whose solution is not obvious.

<sup>149</sup>Maeder, *supra* note 1, at 87. Recall the discussion about the prices of Genzyme's Ceredase, for instance.

<sup>150</sup>Hogan, *supra* note 89, at 532.

<sup>151</sup>EMA Report, *supra* note 59, at 34.

<sup>152</sup>Maeder, *supra* note 1, at 87. For a general discussion on prescription drugs in the US, cf. John D. Pinzone, *The Affordable Prescription Drugs Act: a Solution for Today's High Prescription Drug Prices* 16 J.L. & Health 145 (2001-2002).

<sup>153</sup>Hogan, *supra* note 89, at 536-537. The author makes clear that these recommendations are "problematic".

<sup>154</sup>*Id.* at 537. As an example, Hogan cites the fact that in 1990, aerosol pentamidine for AIDS retailed for \$26 per vial in Europe, while the price in the US went from \$120 to \$200. *Id.* at 538. However, orphan drug prices are even higher in Japan. Gina M. Cavalier, *Pushing Parentless Pharmaceuticals: Toward an International Home for "Orphan Drugs" and a Cure for "Zebra" Diseases* 27 Law & Pol'y Int'l Bus. 447, 458 (1996).

The problem of the clash between orphan legislation and pharmaceutical cost containment is considerably larger in the European Union, since each individual member State has its own Social Security and reimbursement policies, as well as a price control scheme of its own. In this context, two proposals tending to harmonization have been suggested. First, EMEA put forward the establishment of some harmonized form of assessment of therapeutic value and pharmacoeconomic evaluation of each authorized orphan medicinal product<sup>155</sup>, which has not been implemented so far. Second and last, Directive 89/105<sup>156</sup> attempts to achieve a greater degree of transparency by requiring national governments to rationally explain any price, profitability or reimbursement limits<sup>157</sup>. However, the above-cited EMEA Report includes in its Annex 5 a study on the availability and pricing of designated orphan medicinal products in the Community, and its results show a “wide heterogeneity” of prices amongst the 15 countries<sup>158</sup>. It appears as evident that the actual efforts towards homogeneous costs are not enough to achieve the purported goal. Of course, a Community policy on health care is still far from being even considered by the Union in the short term, but however, a better coordination and transparency of national policies must be encouraged.

#### 4.5.

#### The True Orphans: Neglected and Tropical Diseases<sup>159</sup>.

The pharmaceutical and biotechnological research developments that have taken place over the last three decades have been basically addressed to cure diseases and conditions whose patients are mostly located in developed countries, while communicable diseases that are still the main cause of mortality and morbidity in the tropical countries received only marginal attention<sup>160</sup>. The causes happen to be pretty obvious: most efforts by the pharmaceutical industry have been and actually are geared toward diseases that may be able to generate economic profits (i.e. cardiovascular disorders, cancer and neuro-degenerative disease, basically)<sup>161</sup>. However, orphan drug initiatives might arguably constitute an opportunity for these tropical

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<sup>155</sup>EMEA Report, *supra* note 59, at 15.

<sup>156</sup>Council Directive 89/105 of 21 December 1988, Relating to the Transparency of Measures Regulating the Pricing of Medicinal Products for Human Use and their Inclusion in the Scope of National Health Insurance Systems (OJ L 40).

<sup>157</sup>Hogan, *supra* note 89, at 553.

<sup>158</sup>EMEA Report, *supra* note 59, at 62-66.

<sup>160</sup>Patrice Trouillier et al., *Is Orphan Drug Status Beneficial to Tropical Disease Control? Comparison of the American and the Future European Orphan Drug Acts* Vol. 4, N. 6 Tropical Medicine and Int'l Health, 412, 412 (1999). As an example, of the approximately 1450 new molecular entities commercialized worldwide between 1972 and 1997, only 13 (less than 1%) were for tropical diseases. *Id.* at 413.

<sup>161</sup>*Id.* at 412.



and neglected diseases to obtain an effective cure through research efforts carried in developed countries and for the mentioned imbalance to be solved<sup>162</sup>. As, Trouiller puts it, “the present profit-driven system is unable to keep pace with current and evolving needs in tropical medicine and policies such as those used for orphan drugs could turn out to be the acceptable dace of disease-driven commerce [...]”. When the market does not provide such treatments, it is the role of society to take appropriate steps”<sup>163</sup>.

Both the US and the EU regulatory frameworks allow for medicines intended to cure third-world diseases to qualify for orphan status by limiting the scope of prevalence required among the designation criteria to either a given ratio or a global number of patients in the United States or in the Community. Thus, ailments which are uncommon in those territories (below the statutory thresholds to gain orphan designation), but extremely frequent in other regions of the world, may be eligible for protection under the Orphan Drug Act or the European Regulations<sup>164</sup>. Hence, the fact that patient population caps refer only to these areas opens the door for widespread conditions to be considered “rare diseases” and thereby receive attention by orphan drug laws<sup>165</sup>. In fact, some progress has been made in this direction, and FDA has approved as orphan products drugs treating malaria, leprosy and African sleeping sickness<sup>166</sup>. The younger European legislation had the opportunity to include an express reference to neglected diseases, but refused to do so, even though this issue was addressed throughout the entire legislative process since its very early stages in the 80s<sup>167</sup>. Provided that the EU law is almost identical when dealing with designation criteria to that of the US, it seems that the same modest results achieved by the Orphan Drug Act will be reached by the European regulation.

However, neither regulatory framework is under current conditions capable of substantially changing the traditional reluctance by pharmaceutical industries to invest in. Keep in mind that exclusive marketing protection tends by its own nature to higher prices, and often those will be well beyond of what poor countries

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<sup>162</sup>Take into account, as a useful information to ascertain the magnitude of the disproportion, that there is a 13-fold greater chance of a drug being commercialized for central-nervous-system disorders or cancer than for a neglected disease. Patrice Trouillier et al. *Drug Development for Neglected Diseases: a Deficient Market and a Public-Health Policy Failure* 359 *Lancet*, 2188 (2002).

<sup>163</sup>Trouillier et al., *supra* note 160, at 419.

<sup>164</sup>The Communication from the Commission on Regulation 1441/2000 on Regulation 141/2000, clearly states that “the prevalence of the disease or condition outside the Community has no influence on the interpretation of [the designation criteria]”. Communication from the Commission, *supra* note 49, at 2.

<sup>165</sup>It seems that Congress had this idea in mind when it drafted the Orphan Drug Act in 1983. Pulsinelli, *supra* note 5, at 343-344.

<sup>166</sup>Haffner, *supra* note 133, at 600. AIDS drugs (9% of the total orphan drug designations. Milne et al., *supra* note 11, at 12) are not taken into account, due to the high prevalence of the HIV infection in developed countries.

<sup>167</sup>Trouillier et al., *supra* note 160, at 416-417.

and their populations can afford. Therefore, some kind of reform is needed to extend the success of orphan drug laws to patients suffering from common diseases in the third world, which represent 90% of the global burden of disease. Specific measures such as prioritization or identification of diseases considered neglected among all rare conditions, fast-track regulatory review, preference for grants and subsidies, international harmonization of regulations or extension and transferability of exclusive marketing rights, are proposed for amending both the Orphan Drug Act and the European laws<sup>168</sup>. In Europe, EMEA has expressly recognized the problem posed by neglected diseases and proposed intervention in the field “consistently with other community action programs in that area”<sup>169</sup>. A statutory reform is essential to provide these “true orphans” with adopters.

#### 4.6.

#### Global Responses: the Need for Coordination.

The pharmaceutical market has become more and more globalized, while the responses from the regulatory sphere remain basically state-based. In this integrated market, the more than 10,000 pharmaceutical producers operate globally in most cases, and their products are available in almost all countries in the world<sup>170</sup>. Besides, 80% of pharmaceutical turnover is produced in the OECD countries (which include all EU member states and the US)<sup>171</sup>.

In a context as that described above, some experts have put forward the necessity of setting up an “integrated global drug approval mechanism”<sup>172</sup>. The EMEA model is itself a good example of how national authorities can be coordinated by and act jointly with a supranational authority. However, the creation of a global authority for orphan drug regulation or, more generally, drug overview, is an utopia in the midterm, and other, more modest alternatives should be devised. Currently, the sounder alternative is the strengthening of collaborative agreements between different national authorities, such as the one implemented between the FDA and its Australian counterpart<sup>173</sup>. This would avoid a considerable amount of uncertainty for sponsors,

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<sup>168</sup>Milne et al, *supra* note 11, at 46-59.

<sup>169</sup>EMEA Report, *supra* note 59, at 15.

<sup>170</sup>Hogan, *supra* note 89, at 546.

<sup>171</sup>*Id.* at 547.

<sup>172</sup>*Id.* at 559.

<sup>173</sup>*Cf.* the discussion in Section 2.2. However, as Hogan asserts, “the FDA has been particularly reluctant to relinquish ultimate control over the drug review processes” *Id.* at 560.

as well as some of their costs (repetitive clinical trials with different standards and the like). Besides, the close similarities between the different regulatory frameworks constitute a good starting point for a deeper harmonization of the approval processes by creating common international standards<sup>174</sup>. At least some modest steps towards harmonization may be foreseen, such the establishment of uniform rules on clinical trials like those discussed at the International Conferences on Harmonization<sup>175</sup> or the issuance of protocols favoring the flux and dissemination of information between regulators and experts worldwide<sup>176</sup>. Anyway, a more complete harmonization appears to be an increasingly important objective for regulators to respond to the reality they try to monitor, which inevitably tends to a global market.

#### 4.7.

##### **Brief Considerations on EU-Specific Problems.**

Finally, some concise considerations must be made with regard to two particular issues that arise exclusively in the European Union regulatory framework. First, reference will be made to the particular structure of the European scheme and, in particular, the two-level enforcement format (States-Community bodies). Second, the lack of both a comprehensive grant program and a tax system that may widen considerably the spectrum of incentives can be a serious handicap for the European orphan drug laws.

One of the serious challenges that the European orphan drug regulation must tackle is the existence of two levels of decision and enforcement, that managed by the Community entities (COMP, EMEA, Commission) and that under the supervision of national authorities<sup>177</sup>. This double-channel structure contrasts with the simple and effective US design: a single and powerful body, the Federal Drug Administration through the Office of Orphan Products Development (OOPD). The alternative between the centralized procedure on one hand and the national procedures via mutual recognition within the Community is good principle to harmonize the European system. However, two main risks exist: first, the existence of at least 16 centers of decision and review may water down the huge amount of information and expertise that orphan drug

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<sup>174</sup>In fact, the WHO has held several International Conferences on Harmonization on the technical requirements for drug registration. Cavalier, *supra* note 154, at 466.

<sup>175</sup>*Id.* at 466. The author is pessimistic about the possibility that significant substantial progresses towards full harmonization may be made, and instead encourages at least some less ambitious steps. This seems also to be the intention of the European regulatory authorities. EMEA Report, *supra* note 59, at 15-16.

<sup>176</sup>*Id.* at 467-473.

<sup>177</sup>In Spain, for instance, the regulatory body is the Spanish Drug and Medicinal Products Agency (“Agencia Española de Medicamentos y Productos Sanitarios”).

and rare diseases regulation require; second, notorious differences may exist among countries in terms of drug availability. Furthermore, both hazards may become more intense after the enlargement scheduled for May 1<sup>st</sup> 2004, when 10 more countries will join the EU. The first potential risk seems to have been averted though an intense cooperation among authorities and the creation of a European network of experts to channel information dissemination and to assist COMP and CPMP<sup>178</sup>. The second hazard appears to have led to practical disparities among countries; the EMEA Report published in April 2003 established that even the first five orphan products approved by the centralized procedure (therefore, not even by national authorities), presented striking differences in terms of their availability in the 15 member states<sup>179</sup>. If this happens with marketing authorizations applying in the entire EU territory at a time, the perspectives for mutual recognition to provide great heterogeneity must be clearly pessimistic. Only better coordination and expedited approvals may solve what constitute a serious disadvantage *vis-à-vis* the American procedures.

Another serious handicap for the development of the European framework is the absence of two categories of incentives that are present in the United States and are responsible in a significant proportion of the success of the Orphan Drug Act. These key incentives include the worldwide-admired FDA grant program and the tax legislation which provides different kinds of credits and reductions. The FDA grant program has funded 25 rare disease treatments that later became marketed orphan drugs<sup>180</sup>, and in 2002, the House Commerce Committee voted unanimously to boost the budgetary appropriation allocated to the development of treatments for rare diseases, authorizing \$25 million annually for 4 years<sup>181</sup>. There is no fair comparison with what is being done on the other side of the Atlantic, where grant programs for orphan drug development are embodied in larger campaigns to fund scientific research and where the amounts are considerably lower<sup>182</sup>. In light of all these considerations, the fee exemptions and protocol assistance in the European Union, should be coupled with an specific grant program similar to that applied in the US<sup>183</sup>.

The situation with tax credits is even worse. The EU bodies lack authority to take decisions on tax issues,

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<sup>178</sup>EMEA Report, *supra* note 59, at 28-29.

<sup>179</sup>For instance, in Belgium only 1 of these products was available when the survey was conducted, while all the 5 drugs were already marketed in Austria or the UK. *Id.* at 62-66.

<sup>180</sup>Haffner, *supra* note , 28 at 39.

<sup>181</sup>Daniel B. Moskovitz, *Federal and State Laws and Regulations Affecting Managed Care* 14(10) Drug Benefit Trends, 13-14 (2002). Since 1983, more than \$67.5 million has been allocated among more than 234 studies. Haffner, *supra* note , at 594. Clinical trials are normally awarded grants from \$100,000 to \$200,000 per year in direct costs for up to 3 years. *Cf.* <<http://www.fda.gov/orphan/grants/faq.htm>>.

<sup>182</sup>The 4<sup>th</sup> and the 5<sup>th</sup> Framework Programs mentioned in Section 2.3 provided funding for rare diseases research since 1994 up to a total of Å8.65 and Å15.6 million respectively. Hansen, *supra* note 37, at 43.

<sup>183</sup>The 2003 EMEA Report made exactly this suggestion. EMEA Report, *supra* note 59, at 14.

which are tied to the sovereignty of member states. Only a few European countries (France, the UK and the Netherlands) have amended their own legislations to include tax credits for orphan research and development<sup>184</sup>. This response is still weak and must be completed by other fellow members as soon as possible, in order for the European pharmaceutical and biotechnological industry to compete in equal terms with their American counterparts. Furthermore, tax benefits contribute to drop industry costs, and therefore, they may trigger lower prices for orphan drugs. However, it must be noted that the American tax credit scheme<sup>185</sup> has been criticized for being “ineffective” in the US, so these attacks must be carefully considered by European governments when designing their own tax models<sup>186</sup>.

## 5.

### Conclusion.

Orphan drug laws have made great contributions towards the cure of millions of people suffering from uncommon and frequently life-threatening diseases since their first exponent was enacted in the US in 1983. By providing various incentives for the industry to adopt these “orphans”, research and commercialization have been considerably improved.

The success of the Orphan Drug Act and ancillary legislation was such that countries all over the world have passed statutes with similar purposes and almost identical content. The European Union joined this group of orphan legislators in 2000, after several years of study and debate. However, since the very early stages of the application of the American legal architecture, some critiques have been arising, critiques that in most cases can be extended to the more recent orphan drug laws as well. This is surely the case of the EU Regulations, that in general terms suffer from the same caveats of their American counterpart. For a long time, what this paper calls “orphan blockbusters” and the abuses by some sponsors attracted most of the attention of the literature. Nevertheless, some new challenges have been put forward by the scientific community and various commentators; among them, the advocated extension of orphan legislation to cover remedies for third-world diseases and the need for international coordination in the field deserve special consideration. Although the

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<sup>184</sup>*Id.* at 39-40.

<sup>185</sup>As it was described in Section 2.1, tax credits amount to 50% of the total amount of money spent on clinical trials.

<sup>186</sup>Pulsinelli mentions as the main caveats of the actual system in the US the exclusion of animal trials, the fact that the credit cannot be carried forward to future years or backward to past tax periods, and the requirement that the benefited company must be “carrying on a business”. Pulsinelli, *supra* note 5, at 337-338. Pointing to the same direction, *cf.* Henry, *supra* note 117, at 636.

same controversies that have taken place in the US may be foreseen in Europe, it is necessary to recognize that the European legislators attempted to settle some of them before they arise, and that is the case of the revocation of market exclusivity laid down in Regulation 141/2000, which constitutes a serious but still untested attempt to avoid profitable orphans.

Orphan drug laws were initially conceived as an instrument for society to fill the void left by market in a socially-sensitive area such as the cure of rare diseases and the right to health, no matter what nature (and the prevalence) of the condition one is afflicted with. In order to achieve this purpose, any orphan drug law must strike a fair balance between competition and innovation, which has been achieved to a high degree in both the US and the EU. However, some improvements may be made and some new situations may be confronted, as this paper attempted to put forward. The words used by Rohde referring to the US Orphan Drug Act may be extended to the EU Regulations as well: “with ‘fine tuning’ to address the criticism addressed at certain of its provisions, the Act can be a more efficient engine of innovation”<sup>187</sup>.

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<sup>187</sup>Rohde, *supra* note 19, at 143.